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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/764,712	BRENNAN ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-24* is/are pending in the application.

4a) Of the above claim(s) *12-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,11 and 15-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 4/30/2007.

1. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Status of the Claims

Claims 10-24 are currently pending.

2. Claims 12-14 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 4/20/2006.

3. Claims 10, 11, 15-24 are examined herein.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 10, 11, 15-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The broadest claims are drawn to a method of treatment that encompasses the administration of ***any*** compound that is an antagonist of MSH biological activity. Dependent claims specifically indicated that the antagonist is a fragment of MSH that has MSH antagonist action or a homologue of MSH. Therefore, in their broadest embodiments the claims encompass a genus of compounds comprising a very large number of molecules, possibly millions, considering every possible MSH antagonist including every possible fragment and homologue molecule having MSH antagonist activity as well as every non-peptide antagonist, such as every small molecule antagonist.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (See MPEP 2100-164)

The written description guidelines note regarding such genus/species situations that "Satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) Here, the application discloses two specific MSH antagonists

which are MSH fragments. They are SEQ ID NO: 5 and SEQ ID NO: 6 (see page 30). The specification also discloses general formulas (1) and (2) on pages 31 and 32, which are formulas for cyclic MSH antagonists. However, the specification does not disclose any antagonists other than those indicated. Furthermore, although the formulas indicate a structure-function relationship for all of the molecules encompassed by the formulas, the claims are not limited to antagonists of these formulas. Accordingly, on of skill in the art would not be able to readily envisage the MSH antagonists that are MSH fragments or homologues, other than those that meet the structural limitations of Formula (1) and Formula (2) (including SEQ ID NO: 5 and SEQ ID NO: 6) without performing additional experimentation.

Therefore, the claims fail to meet the written description requirement because the claims encompass molecules which are not sufficiently described in the specification.

Claims 10,11, 15-24 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

> *Wands* states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The invention is drawn to methods of treating insulin resistance or diabetes caused by insulin resistance by administering an antagonist of MSH biological activity to a patient. Therefore, the invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims are very broad with respect to the genus of MSH antagonist compounds encompassed by the claims. As indicated above, the claims encompass administering any antagonist of MSH activity. As such, the claims could potentially encompass thousands, if not millions of different compounds, including compounds that have yet to be discovered or created.

The unpredictability of the art and the state of the prior art

As indicated above, the claims are drawn to methods of treating insulin resistance or diabetes caused by insulin resistance by administering an antagonist of MSH biological activity to a patient. Therefore, in order for the claimed method to work in a predictable manner, the antagonists encompassed by the claims must be able to ameliorate the effects of insulin resistance (claims 10, 11, 15-19 and 21-23) and diabetes caused by insulin resistance (claim 20). However, the prior art teaches that agouti, an antagonist of MSH biological activity, actually increases insulin resistance and a form of type II diabetes associated with insulin resistance.

For instance, WO 97/47316 (Lee et al.; cited by Applicants in the 3/2004 IDS) teaches,

> "The agouti protein is a gene product expressed in mice that is known to be involved in determining coat color, but also thought to play a role in obesity when its normal expression pattern is de-regulated an the protein is ubiquitously expressed... it has been observed that agouti antagonizes the MSH-induced activation of two melanocortin receptors." (see page 2, first paragraph)
>
> "Ectopic expression of the normal, wild-type, agouti protein in transgenic mice result in obesity, diabetes, and the yellow coat color commonly observed in spontaneous obese mutants." (see page 3, last paragraph)
>
> "Agouti has been reported to be a competitive antagonist of αMSH binding to the MC1-R and MC4-R in vitro and the authors speculated that ectopic expression of agouti may lead to obesity by antagonism of melanocortin receptors expressed outside the hair follicle. In this regard a number of theories have been proposed to account for the induction of obesity by ectopic expression of agouti. For example agouti protein expression skeletal muscle may result in insulin resistance, hyperinsulinemia and obesity via elevation of Ca^2+ levels..." (see page 4, lines 7-17).

Furthermore, Klebig et al. (PNAS 92:4728-4732; 1995) teaches that ectopic expression of the agouti gene in transgenic mice causes obesity, features of type II diabetes associated with insulin resistance, and yellow fur. Specifically, Klebig teaches, "Transgenic mice of both sexes have yellow fur, become obese, and develop hyperinsulinemia." (See abstract). Klebig also teaches that agouti is an antagonist of αMSH activity (see page 4728, second column).

Therefore, the prior art indicates that antagonists of MSH activity are associated with increased obesity and diabetes associated with insulin resistance. As such, one of skill in the art would not expect the MSH antagonists to be able to treat insulin resistance without performing additional experimentation.

Working Examples and Guidance in the Specification

The specification and working examples disclose the production of a transgenic mouse that does not express the pomc gene. It is noted that the pomc gene is responsible for the expression of αMSH (e.g., see page 11). The specification indicates that the pomc knock-out

mice are protected from the development of obesity-induced insulin resistance and that administration of MSH to the mice nearly normalizes the glucoregulatory response in mice (see Example 2, page 52). However, the specification does not disclose that any specific antagonists of MSH biological activity were identified, nor does it disclose that an antagonist of MSG biological activity was able to treat insulin resistance or diabetes associated with insulin resistance in any patient (including the knock-out mouse or a human subject).

Quantity of Experimentation

Considering that the prior art indicates that MSH antagonists (specifically agouti) increases insulin resistance and diabetes associates with insulin resistance, and in view of the limited working examples and guidance provided in the specification, additional experimentation would be required. The additional experimentation would amount to trial and error testing of MSH antagonists for their ability to treat insulin resistance and diabetes associated with insulin resistance which would amount to an inventive step over the prior art.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the nature of the invention, the breadth of the claims, the unpredictable nature of the invention as recognized in the prior art, the limited amount of working examples and guidance provided, and the high degree of skill required to practice the invention, it is concluded that the specification does not provide an enabling disclosure for the instant claims. Therefore, additional experimentation is required before one of skill in the art could make and

use the claimed invention. The amount of additional experimentation required to perform the broadly claimed invention is undue.

4. Claim 24 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

MPEP §2163.06 notes:

If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

MPEP §2163.02 teaches that:

Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

MPEP §2163.06 further notes:

When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure.

The instant claim is drawn to the method of claim 11 wherein the antagonist is a fragment of MSH or a homologue of MSH having antagonist action wherein the antagonist comprises a substitution of Phe at position 7 of MSH with another amino acid. Applicants refer to page 30 for support for the new claim. However, the specification at page 30 only discloses one specific MSH antagonist with a substitution of Phe7 with another amino acid: the antagonist disclosed as SEQ ID NO: 5. Therefore, the specification only provides support for one specific antagonist, where Nal is substituted for Phe7, while the instant claim encompasses a genus of antagonists where the antagonist can have any number of substitutions as long as the antagonist includes a substitution of Phe7 with any amino acid. The disclosure of a single specific substitution does not provide support for the genus of substitutions and variants encompassed by the new claim.

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claim 24 is also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

Response to Arguments

1. Applicant's arguments filed 1/16/07 have been fully considered but they are not persuasive.

2. With respect to the Written Description rejection, applicants argue that pages 30-32 describe numerous exemplary MSH analogs that may be useful as antagonists. Applicants also refer to U.S. 5,731,408 which reports prior structure function analysis on the affinity and potency of MSH at the MSH receptor. Applicants contend that these studies resulted in the identification of a number of MSH antagonists. Applicants also contend that a review article (Holder et al.) teaches that in 1995 modification of the Phe7 amino acid of MSH results in antagonist action.

3. In response, it is noted that the specification at pages 30-32 disclose two specific antagonists (SEQ ID NO: 5 and SEQ ID NO: 6) as well as Formulas (1) and (2) which are two general formulas each for a genus of cyclic peptide antagonists of MSH. Furthermore, the '408 patent only appears to disclose two specific antagonists, which are the antagonists disclosed in the instant application as SEQ ID NO: 5 and SEQ ID NO: 6 (see Table II and Table III). It is also noted that Table III only discloses two antagonists, the rest being agonists. Therefore, the specification and the '408 patent only provide description of the MSH antagonists that are SEQ ID NO: 5 and SEQ ID NO: 6 as well as the compounds that meet the structural requirements of Formula (1) and Formula (2). It is acknowledged that Holder et al. does indicate that modification of the Phe7 amino acid of MSH results in antagonist action. Holder et al., however, does not indicate that the genus of MSH antagonists encompassed by the instant claims were known and available at the time the invention was made such that one of skill in the art would readily recognize the MSH antagonists encompassed by the instant claims without performing additional experimentation. However, the instant specification does not appear to contemplate an MSH that has a modification of the Phe7 amino acid, as taught by Holder. Therefore, limiting the claims to the antagonist that are SEQ ID NO: 5 and SEQ ID NO: 6 as well as the compounds

that meet the structural requirements of Formula (1) and Formula (2) would obviate this rejection.

4. With respect to the enablement rejection, Applicants refer to the declaration pursuant to 37 C.F.R. §1.132 by Dr. Miles Brennan, inventor of the present invention. The declaration of Dr. Brennan under 37 CFR 1.132 filed 1/16/2007 is insufficient to overcome the rejection of claims 10,11, 15-24 based upon insufficiency of disclosure under 35 U.S.C. 112, first paragraph as set forth in the last Office action for the following reasons. The claimed invention must be enabled by the disclosure of the specification at the time of filing. The declaration of Dr. Brennan described experiments where an MSH antagonist referred to as "JRH-322" was administered to hyperglycemic (ob/ob) mice in order to demonstrate that the administration of an antagonist of MSH biological activity ameliorates the effects of insulin resistance and diabetes caused by insulin resistance. However, the antagonist "JRH-322" is not disclosed in the instant specification and does not appear in the prior art until 2003 (see Holder et al. Ann. N.Y. Acad. Sci. 2003), three years after the effective filing date of the instant application. Accordingly the evidence presented does not demonstrate that the specification enabled the claimed invention at the time of filing. Furthermore, even if JRH-322 was a known MSH antagonist at the time of filing, the evidence presented would only indicate the JRH-322 decreases blood glucose levels in hyperglycemic (ob/ob) mice (an art accepted model of insulin resistance). The evidence does not demonstrate that the claims are enabled to their full scope. Therefore, the declaration by Dr. Brennan is insufficient to overcome the rejection.

Conclusion

5. **No claim is allowed.**

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Monday-Thursday 8:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. E. Angell/
Primary Examiner
Art Unit 1635